Medical and Pediatric Oncology 28:462–464 (1997)

Letter to the Editor: Improvement of Langerhans' Cell Histiocytosis and Pancreatitis by Alpha-interferon

Interferon (IFN) possesses both antiviral activity as well as a variety of biological activities, including cell growth inhibition, immunosuppressive effects, enhancement of macrophage, natural killer cell, and neutrophil functions, and cell differentiation-inducing activity [1–3]. These biological functions of IFN also produce its antitumor activity. IFN is also involved in the pathogenesis of various diseases, such as collagen vascular disease, insulin dependent diabetes mellitus, fulminant hepatitis, pancreatitis, nephritis, multiple sclerosis, allergic disease, and atherosclerosis [3].

We experienced a 2-year-old boy with Langerhans' cell histiocytosis (LCH), who was treated by alpha-IFN with partial success and later developed chemically-induced pancreatitis. The diagnosis was made on the basis of the clinical symptoms such as seborrheic skin lesions, erosions of the gingiva and perianal mucosa, and huge osteolytic lesions of the sphenoid and the histopathologic findings including a positive S100 and negative KP1. When a total alpha-IFN dose of 370 million units as a partially successful treatment was attained, the amylase concentration became mildly elevated (149 IU/L) (43 < normal < 131). An additional IFN dose of 18 million units was administered with close monitoring of the amylase concentration. When the amylase concentration increased to 155 IU/L, IFN was discontinued. The patient complained of mild back pain 3 days later. Four days after the onset of pain the amylase was 271 IU/L, and 3 days later, it decreased to the normal range without specific treatment. After this episode, accumulational effect of alpha-IFN was occurred: a prolonged increase of amylase over the next 2 weeks, after a single injection of alpha-IFN and subsequent short time increase of the amylase after a febrile upper respiratory infection, after the cessation of alpha-IFN therapy. There were no factors which lead to the increase of serum amylase levels such as diet, co-medication, or parotitis.

Two months after the end of alpha-IFN therapy, LCH recurred. Therefore, we instituted therapy with 2–3 mg/m^2/week of vindesine, which also produced an elevation in the amylase concentration after 8 weeks. However, unlike our experience with alpha-IFN, the amylase normalized when vindesine was discontinued for a week, and an accumulation effect of the previous vindesine administration on the amylase concentration was not observed. The vindesine treatment resulted in an improvement in all the patient's clinical symptoms.

The optimal IFN therapy has not been established because the effect of IFN differs among the reports [4–7]. However, since no optimal drug regimen for the treatment of LCH has been proposed and fewer adverse effects of IFN exist as compared with those of antineoplastic drugs, IFN treatment should be attempted. Although IFN-induced pancreatitis has been described, it is infrequent, and the details of its clinicopathology are not well known [8]. Severe acute pancreatitis induced by alpha-IFN requires specific and active treatment [9]. The acute pancreatitis in our patient was not severe and did not require specific treatment, but the amylase concentration remained elevated and rose immediately with subsequent IFN administration. Although the side effects of IFN usually are rapidly reversible upon cessation of therapy, such an accumulation effect of alpha-IFN has not been previously reported [10]. Additionally, a febrile upper respiratory infection resulted in an elevated amylase concentration during the cessation of IFN, which was suspected to be caused by the intrinsic IFN produced in response to the viral infection during the upper respiratory infection.

Masao Hirose, MD
Division of Transfusion Medicine
University Hospital of Tokushima
Kuramoto-cho 2-50
Tokushima-shi, Tokushima 770, Japan

REFERENCES

1. Nagano Y, Kojima Y: Pouvier immunisant de virus vaccinal inactive par des rayons ultraviolets. C R Soc Biol 148:1700–1702, 1954.
2. Isaacs A, Lindenmann J: Virus interference I. The interferon. Proc Roy Soc (B) 147:258–267, 1957.
3. Imanishi J: IFN-α, β, γ. Jpn J Cancer Chemother 21:2853–2858, 1994.
4. Greenberger JS, Crocker AC, Vawter G, Jaffe N, Cassady JR: Results of treatment of 127 patients with systemic histiocytosis (Letter-Siwe syndrome, Shueller-Christian syndrome and multifocal eosinophilic granuloma). Medicine-Baltimore 60:311–338, 1981.
5. Jakobson AM, Kreuger A, Hagberg H, Sundstrom C: Treatment of Langerhans cell histiocytosis with alpha-interferon. Lancet ii: 1520–1521, 1987.
6. Sato Y, Ikeda Y, Ito E, Miyano T, Kawauchi K, Yokoyama M, Kamata Y: Histiocytosis X: successful treatment with recombinant interferon-alpha. Acta Paediatr Jpn 32:151–154, 1990.
7. Halton J, Whitton A, Wiernikowski J, Barr RD: Disseminated Langerhans cell histiocytosis in identical twins unresponsive to

recombinant human alpha-interferon and total body irradiation. Am J Pediatr Hematol Oncol 14:269–272, 1992.
8. Stadler WM, Vogelzang NJ, Vokes EE, Charette J, Whitmen G: Continuous-infusion fluorodeoxyuridine with leucovorin and high-dose interferon: a phase II study in metastatic renal-cell cancer. Cancer Chemother Pharmacol 31:213–216, 1992.
9. Sotomatsu M, Shimoda M, Ogawa C, Morikawa A: Acute pancreatitis associated with interferon-alpha therapy for chronic myelogenous leukemia. Am J Hematol 48:211–212, 1995.
10. Sacks SL, Scullard GH, Pollard RB, Gregory PB, Robinson WS, Merigan TC: Antiviral treatment of chronic hepatitis B virus infection: pharmacokinetics and side effects of interferon and adenine arabinoside alone and in combination. Antimicrob Agents Chemother 21:93–100, 1982.

Letter to the Editor: Successful Treatment of Orbital Rhabdomyosarcoma in Two Infants Using Chemotherapy Alone

Álvarez Silván and colleagues recently described two children with orbital embryonal rhabdomyosarcomas successfully treated with chemotherapy alone [1]. Because of the important impact on treatment (fewer late effects in case of no irradiation) we would like to report on two other cases successfully treated with chemotherapy alone.

In October 1987, a 2-year-old girl presented with a short history of right-sided exophthalmus and ptosis. MR-imaging showed an orbital mass with 2.5 cm in diameter extending from the upper right eyelid to the inner parts of the orbita. No bone erosion was seen. A biopsy was performed and revealed embryonal rhabdomyosarcoma. Multiagent chemotherapy was initiated according to the Cooperative German Soft Tissue Sarcoma Study CWS-86 [2]. Over a total treatment period of nine months the patient received five courses of VAIA, each lasting seven weeks and including Vincristine (5×1.5 mg/m^2), Dactinomycin (6×0.5 mg/m^2), Ifosfamide (6×3 g/m^2), and Adriamycin (2×40 mg/m^2). After the first cycle the tumor-size markedly decreased, and after the second cycle there was no evidence of residual disease at CT and MRI. Therefore rebiopsy was not performed and the decision was made not to irradiate. The patient is now—nine years from diagnosis—in persistent complete remission without any impairment to the lens or orbita. The second child, a 9-year-old boy, was admitted in August 1990 because of a tumor in the right orbit with exophthalmus. Partial resection had been performed two weeks ago in another hospital and histologic examination revealed embryonal rhabdomyosarcoma. Postoperative MR-imaging showed residual tumor ($5 \times 1 \times 1.5$ cm) with enhancement of contrast medium and infiltration into the orbit rim. Multiagent chemotherapy was initiated as in the first case and after two courses of VAIA no evidence of residual tumor could be found. Again rebiopsy and irradiation were not done. Chemotherapy was continued for three additional courses. At last follow-up—four years after initial diagnosis—the patient was in a good clinical condition, his right-sided ptosis has been corrected by surgery and there was no evidence of recurrent disease. In accordance to Álvarez Silván and coworkers we believe that patients with embryonal RMS can be successfully managed by chemotherapy alone without mutilating surgery or radiation if there is a *complete* response. This seems to be the case not only in infants, but also in elder children.

H. Lackner, MD
C. Urban, MD
Division of Pediatric Hematology/Oncology
Univ.-Children's Hospital
Auenbruggerplatz 30
A-8036 Graz, Austria

REFERENCES

1. Álvarez Silván AM, Cantón G, Cuevas P, Gutiérrez A: Successful Treatment of Orbital Rhabdomyosarcoma in Two Infants Using Chemotherapy Alone. Med Pediatr Oncol 26:186–189, 1996.
2. Maurer HM, Ruymann FB, Pochedly C: Rhabdomyosarcoma and Related Tumors in Children and Adolescents. CRC Press, Boca Raton, Ann Arbor, Boston, London, 227–241, 1991.

Solicited Comment

Dr. Álvarez Silván and her colleagues from Sevilla, Spain, agree with Dr. Lackner, that only chemotherapy and conservative surgery, could be enough for orbital ERMS in older children.

They have good experience in two infants with rhabdomyosarcoma, treated exclusively with chemotherapy (that included ADR) and conservative surgery. They survived for 5 and 7 years respectively.

In the same series, five out of ten other children with

orbital ERMS treated with conventional treatment, had relapses after chemotherapy and radiotherapy. At that moment they were treated successfully with chemotherapy and conservative surgery. All of them are free of disease between 4 and 6 years, except one patient who has had 3 more relapses, but now is free of disease for more than 1 year.

However, they strongly advise complementary radiotherapy for most children with other localizations of rhabdomyosarcoma. Combined chemo-radio-therapy, using a drug regimen that includes doxorubicin, is given first in cases considered inoperable at diagnosis.

Ana María Álvarez Silván
Chief, Pediatric Oncology Section
Hospital Virgen Del Rocio
41013 Sevilla, Spain